REMARKS/ARGUMENTS

In response to the Final Office Action of November 9, 2005, Applicants request re-examination and reconsideration of this application for patent pursuant to 35 U.S.C. 132.

Claim Status/Support for Amendments

Claims 39 and 42 have been amended. Claims 2-38 were cancelled in a previous response (filed on June 9, 2003). Claims 39-46 are withdrawn from consideration. It is understood that claims 39-46, drawn to the non-elected invention, will remain pending, albeit withdrawn from consideration on the merits at this time. If the examined claim of the Group I invention is deemed to be allowable, rejoinder of the remaining claims (39-46) in accordance with the decision in *In re Ochiai* is respectfully requested; since the remaining claims (39-46) are limited to the use of the biopolymer marker of claim 1 (the examined claim of the elected Group I invention).

Claim 1 is currently under examination. Claims 1 and 39-46 remain pending in the instant application.

No new matter has been added by the amendment to the specification made herein.

The paragraph at page 24 has been amended to correct a

typographical error (luymph to lymph).

No new matter has been added by the amendments to the claims made herein.

Claim 39 has been amended to clearly indicate how the presence of the claimed biopolymer marker is determined from mass spectral profiles. The changes to claim 39 find basis throughout the original disclosure, see, for example, page 38, line 18 to page 40, line 13 and Figures 1 and 2.

Claim 42 has been amended to clarify that the recited Markush group is a group of different mass spectrometric techniques.

Request for Rejoining of Claims

Considering that claims 39-46 are limited to the use of SEQ ID NO:1 a search of these claims would encompass this specific sequence. The instant application is related in claim format to several other applications, both pending and issued, of which serial number 09/846,352 is exemplary. In an effort to maintain equivalent scope in all of these applications, Applicants respectfully request that the Examiner consider rejoining claims 39-46 in the instant application, which are currently drawn to non-elected Groups, with claim 1 of the elected Group under the decision in *In re Ochiai* (MPEP 2116.01), upon the Examiner's determination that claim 1 of the elected invention is allowable

and in light of the overlapping search. If the biopolymer marker of SEQ ID NO:1 is found to be novel, methods and kits limited to its use should also be found novel.

Rejection under 35 USC 101

Claim 1, as presented on October 13, 2005, remains rejected under 35 USC 101 because the claimed invention allegedly has no apparent or disclosed specific and substantial credible utility.

The Examiner states that the Declaration of Lander under 37 CFR 1.132 filed on October 13, 2005 has been fully considered. The Examiner asserts that the Declaration is insufficient to overcome the rejection of claim 1 based upon lack of utility and enablement as set forth in the last Office Action because the copy of Figure 1 filed with the Declaration is allegedly of less clarity than the originally filed Figure 1.

Applicants respectfully disagree with the Examiner's assertion. However, Applicants file a second Declaration herewith wherein the attached copy of Figure 1 will also be forwarded by e-mail to the Examiner such that the figure will not be subjected to the PTO scanning system which may obstruct the clarity of the figure.

The claimed peptide (amino acid residues 2-18 of SEQ ID NO:1) was obtained from Band C1 of the gel shown in Figure 1. Band C1 is

present in lanes 5-8 (as read from the left) which contain samples obtained from patients age-matched with the patients having Alzheimer's disease. However, Band C1 is absent from lanes 1-4 which contain samples obtained from patients having Alzheimer's disease. Thus, the claimed peptide (amino acid residues 2-18 of SEQ ID NO:1) is differentially expressed between Alzheimer's disease and a normal (with respect to Alzheimer's disease), age-matched physiological state.

In order to further illustrate this point, Applicants attach hereto a second Declaration under 37 CFR 1.132. The figure attached to this second Declaration is identical to the figure attached to the previous Declaration. The figure is entitled "DEAE 3 (Elution) AD vs. Age Matched AD(Control)" and represents Figure 1 as originally filed. This figure was produced by scanning the original photograph of the gel. No new matter has been added; this figure is simply a clearer copy of Figure 1 as originally filed and is provided to clarify the presence, absence and differential expression of the claimed biopolymer marker (amino acid residues 2-18 of SEQ ID NO:1). The gel shown in the attached figure does not represent new experimentation; the figure shows a clearer image of the original gel which was made at the time that the experiments described in the instant specification were first carried out.

The Examiner asserts that the Brief Description of the Figures

at page 37 does not contain any disclosure of how fragment 2-18 of SEQ ID NO:1 corresponds to the bands as shown in Figures 1, 3 and 5.

At page 46, lines 11-19 of the instant specification as originally filed, the claimed sequences are identified by molecular weight. Figures 2, 4 and 6 show mass spectral profiles of ions identified by molecular weight. Figures 2, 4 and 6 also indicate the band from which the ion profiled was obtained. For example, Figure 2 shows the mass spectral profile of SEQ ID NO:1, weighing about 1873 daltons and obtained from Band C1 of the gel shown in Figure 1. Thus, contrary to the Examiner's assertions, Applicants respectfully submit that the instant specification as originally filed discloses how to connect the claimed sequences to the bands shown in the gels.

The Examiner states that she fully agrees that identification and selection of reliable biomarkers to diagnose pathological conditions is a known practice. Moreover, identification of a marker that is specifically associated with a particular condition (present/absent or present at specific altered levels as compared to normal control) constitutes a specific and substantial credible utility even if a biological role of the molecule itself is not known or disclosed. However, the Examiner insists that this is not the factual situation in the instant case. The Examiner asserts

that Applicants' invention is predicated on the finding that samples of blood taken from patients suspected of having Alzheimer's disease contain proteins in the forms and amounts that are different from normal control samples. Applicant further extrapolates this result into a diagnostic tool for Alzheimer's disease. The Examiner asserts that it would appear that Applicant provides a single finding and then presents an invitation to experiment to determine the level of differential expression of peptide 2-18 of SEQ ID NO:1 that is diagnostic of Alzheimer's disease, and then to assay if the peptide could be used to diagnose Alzheimer's disease, such as to distinguish Alzheimer's disease from a normal state and from other similar neurodegenerative conditions, as well as to treat Alzheimer's disease.

Applicants respectfully assert that the Examiner's interpretation of the invention is not entirely correct.

The instant specification discloses how the claimed biopolymer marker (amino acid residues 2-18 of SEQ ID NO:1) was identified and provides the mass spectral profile of this biopolymer marker (shown in Figure 2) for use as a reference for comparison with mass spectral profiles obtained from unknown samples. Assays using this mass spectral profile as a reference can be immediately applied and thus, in compliance with the utility standard, the instant invention is useful in its currently available form.

The claimed biopolymer marker (amino acid residues 2-18 of SEQ ID NO:1) was identified in the following manner:

Proteins contained within the sera samples are often too large (>3kd) to be effectively resolved by most forms of mass spectrometry, thus the samples can first be resolved by polyacrylamide gel electrophoresis. Samples to be compared, e.g. disease state versus normal, are usually run side by side in the gel. Once the proteins have been resolved and visualized with stains, the proteins (represented by bands) that differ between the two compared states (disease versus normal) can be excised from the gel for further purification and identification. The excised bands are then cleaved by enzymes into fragments smaller than 3kd and the fragments are further purified by some form of chromatography; C18 ZIPTIP, column flow-through, column elution stream, and/or column scrub stream. See the instant specification as originally filed at page 25, line 16 to page 26, line 22; page 37, line 18 to page 40, line 13; for specific chromatographic protocols, page 40, line 15 to page 46, line 10. The purified fragments (peptides) are then sequenced by mass spectrometry. These peptides are fragments of the original protein obtained from the sample are sequenced to form a spectral pattern composed of parts of the peptide. The spacing in terms of mass between the parts of the peptide is unique and is referred to as the "fragmentation pattern". See the instant

specification as originally filed at page 39, lines 4-17.

The proteolytic cut sites within a protein can be predicted from the translated amino acid sequence. The mass of the peptides that result from the predicted cutting can be calculated and the theoretical fragmentation pattern determined. The mass spectral profile, i.e. peptide mass and fragmentation pattern, obtained from the experiments, is compared to a database containing theoretical fragmentation patterns and is identified by best match. See the instant specification as originally filed at page 39, line 18 to page 40, line 13. It is important to point out that mass spectral profiles are reproducible; many have been published and may be used as references for identification of unknowns.

The mass spectral profile of the claimed biopolymer marker (amino acid residues 2-18 of SEQ ID NO:1) provided in Figure 2 can be compared to mass spectral profiles obtained from unknown samples. The mass spectral profile of the claimed biopolymer marker has an ion peak at about 1873 daltons and the presence of the biopolymer marker is confirmed by the identification of this ion peak in a mass spectral profile obtained from a sample. Identification of this mass spectral profile links the sample to Alzheimer's disease, for example, if the mass spectral profile shown in Figure 2 is found in a mass spectral profile obtained from an unknown sample, then the sample is linked to Alzheimer's

disease.

Thus, contrary to the Examiner's assertion, the instant invention is complete and usable as described in the original specification. Applicants do not present an "invitation to experiment". The instant specification already evidences that the claimed biopolymer marker can distinguish Alzheimer's disease from a normal physiological state and provides a tool, the mass spectral profile shown in Figure 2, which can be used by one of ordinary skill in the art as a reference for comparison with mass spectral profiles obtained from unknown samples. Since the instant specification provides the information and the tool required to use the claimed peptide as a marker for Alzheimer's disease, there is no need for one of skill in the art to experiment to determine the level of differential expression of the claimed biopolymer marker or to assay to see if the peptide could be used to diagnose Alzheimer's disease.

Thus, contrary to the Examiner's assertion, the situation in the instant invention is akin to the situations in the references cited in the prior Response (for example, the Patterson reference) wherein a marker, amino acid residues 2-18 of SEQ ID NO:1, is specifically associated with Alzheimer's disease as being absent in samples obtained from patients having Alzheimer's disease and present in samples obtained from patients age-matched with the

Alzheimer's disease. Accordingly, Applicants respectfully submit that the instant invention has a specific and substantial credible utility as a marker for Alzheimer's disease.

The Examiner asserts that the instant specification presents several definitions of a "biopolymer marker", essentially that it is a polymer of biological origin which can be present/absent/down-regulated/up-regulated with respect to a disease condition. However, the Examiner asserts that according to Webster's dictionary a "marker" is "one that marks or distinguishes". The Examiner further asserts that there appears to be no information presented in the instant specification as to what constitutes the finding of a peptide 2-18 of SEQ ID NO:1 in a sample. For example, if a peptide 2-18 of SEQ ID NO:1 was found in a sample obtained from a patient, what would that mean to the skilled practitioner? Does it mean that a patient has AD, or is at risk of developing the disease? The Examiner asserts that the instant specification fails to provide any factual evidence that finding of a peptide 2-18 of SEQ ID NO:1 could lead to any meaningful determination for diagnosis or treatment of Alzheimer's disease.

First, it appears that the Examiner is suggesting that the definition of "biopolymer marker" presented in the instant specification is somehow incorrect and/or inadequate. According to the web site dictionary.com, in which definitions are compiled from

many dictionaries, the term "marker" with respect to medicine is a physiological substance that may indicate disease when present in abnormal amounts in the serum and/or something that serves to identify, predict or characterize (see attached definition of "marker" as obtained from dictionary.com; reference 1). Additonally, according to the website dictionary.com, the term "biomarker" refers to a specific physical trait used to measure or indicate the effects or progress of a disease or condition and/or a distinctive biological or biologically derived indicator of a process, event, or condition (see attached definition of "biomarker" as obtained from dictionary.com; reference 2).

The claimed peptide (amino acid residues 2-18 of SEQ ID NO:1) was obtained from Band C1 of the gel shown in Figure 1. Band C1 is present in lanes 5-8 (as read from the left), however, Band C1 is absent in lanes 1-4. The samples in lanes 1-4 were obtained from patients having Alzheimer's disease and the samples in lanes 5-8 were obtained from patients age-matched with the Alzheimer's disease patients. The claimed peptide is present in normal (with respect to Alzheimer's disease), age-matched control patients and absent in Alzheimer's disease patients and as such may indicate a prediction of Alzheimer's disease in the age-matched control group (see the instant specification at page 11, lines 9-13). Thus, contrary to the Examiner's assertion, one of ordinary skill in the

art can make a meaningful determination regarding Alzheimer's disease from the information presented in the instant specification without any additional experimentation. Furthermore, since the claimed peptide (amino acid residues 2-18 of SEQ ID NO:1) predicts a condition, it is clearly well within both the definition of "marker" presented in the instant specification (see for example, page 11, lines 9-13) and the definition available in the art (according to dictionary.com; see references 1 and 2).

The Examiner acknowledges that the claimed peptide (amino acid residues 2-18 of SEQ ID NO:1) is differentially present in the samples of patients suspected of having Alzheimer's disease, however, the Examiner strongly disagrees that the showing of differential expression of the claimed biopolymer marker is sufficient to establish the credibility of the stated utility for the claimed biopolymer marker. One skilled in the art readily appreciates that many proteins are differentially expressed between healthy and "diseased" tissues, however, not all of these proteins constitute biomarkers, as molecules that allow to distinguish between disease vs. healthy.

The Examiner asserts that differential expression as indicated in Figure 1 is a relative term based on the levels found in the samples analyzed. One skilled in the art readily understands that in order to use the claimed peptide as a biomarker for Alzheimer's

disease, a point of reference that is critical for diagnosis with respect to the level of differential expression of the claimed peptide must be disclosed. The Examiner asserts that in the absence of this critical information, it is unclear as to how one reasonably skilled in the art can reasonably determine if the claimed peptide can be used as a diagnostic marker for Alzheimer's disease. Thus, a skilled practitioner would have to resort to a substantial amount of further experimentation in order to practice Applicant's invention. The Examiner further asserts that it is a matter of law that the claimed invention must be useful in currently available form, which precludes any further experimentation in order to be able to practice Applicant's invention.

It appears that the Examiner is requiring Applicants to show evidence that the claimed biopolymer marker (amino acid residues 2-18 of SEQ ID NO:1) is definitively diagnostic for Alzheimer's disease and/or show that it is immediately useful as a marker for Alzheimer's disease.

Applicants respectfully submit that the Examiner is requiring Applicants to meet a standard higher than is necessary to show that an invention has utility.

Applicants remind the Examiner that the utility threshold is not high and that the stringency of evaluating evidence related to

utility is well established. For example, an applicant is not required to provide evidence sufficient to establish that an asserted utility is "true beyond a reasonable doubt". Instead, evidence will be sufficient if, considered as a whole, it leads a person of ordinary skill in the art to conclude that the asserted utility is more likely than not true; MPEP 2107.02 VII. The "definitive" evidence, very focused research and/or further characterization apparently required by the Examiner would provide much more information than what is needed in order to ascertain whether something is more likely than not true. The evidence must simply be convincing for one to conclude that something, in the instant case the usefulness of the claimed peptide as a marker for Alzheimer's disease, is more likely than not true.

As was already established in the previous Response filed on October 13, 2005, one of ordinary skill in the art would recognize differentially expressed peptides to be potential markers for a disease condition. The differential expression of the peptide is the convincing property. Even the Examiner expresses little doubt that the claimed peptide is more likely than not a marker for Alzheimer's disease (page 7 of the Final Office Action mailed on November 9, 2005). Since the utility standard only requires evidence to be convincing rather than fully conclusive and further, since those of skill in the art are convinced that differential

expression identifies biomarkers, then the differential expression of the claimed peptide (amino acid residues 2-18 of SEQ ID NO:1) should be deemed sufficient evidence to convince one of skill in the art that the claimed peptide is more likely than not a marker for Alzheimer's disease, especially in light of the fact that the Examiner herself believes that the claimed peptide is more likely than not a marker for Alzheimer's disease.

The Examiner asserts that there appears to be no evidence presented in Applicant's cited articles that would support a conclusion that any protein that is found to be differentially expressed under a pathological condition, could immediately be used as a marker for that condition.

Applicants respectfully submit that while the particular articles cited in the previous response may not explicitly support such a conclusion, other references available at the time of the invention do. For example, US 6,124,108, issued to Prabhati Ray on September 26, 2000, discloses a protein biomarker for mustard chemical injury (see attached copy of patent; reference 3). Upon electrophoretic separation of an extract of human skin cells, Ray immediately identified a protein band found at 50,000 to 80,000 daltons as a biomarker (see abstract and column 2, lines 1-25). Analogous to the disclosed uses of the biopolymer marker of the instant invention, Ray also indicated that his biomarker can be

used to raise antibodies or may be used in a kit for identifying the presence or absence of the marker (see abstract).

Furthermore, it is important to point out that Applicants filed many other applications drawn to biopolymer markers for various conditions which are similar to the instant application. Many of these applications were deemed to teach useful, enabled inventions and thus, were issued as patents; US 6,890,722 is particularly relevant, see attached front and claim pages; reference 4).

The Examiner asserts that one skilled in the art readily appreciates that detection of differentially expressed proteins represents only the first step in identification of molecules that have a diagnostic potential. The search for a diagnostic marker is usually divided into two steps; the first step being an exploratory search to identify a subset of proteins that may be involved in physiological/pathological processes and the second step, which involves very focused research to confirm that the detected differentially expressed protein can be used as a marker. The Examiner indicates that the instant specification identified a peptide that is differentially expressed between Alzheimer's samples and normal control; however, asserts that there appears no further characterization presented that would lead to the "real world" specific utility of this peptide as a biomarker for AD.

Without this further characterization, the Examiner asserts that Applicant's claimed invention is incomplete. As such, the Examiner concludes that the claimed peptide is only suitable for further research, which constitutes a utility that is not considered a "substantial" utility. The Examiner relies on the decisions in *In re Fisher* 76 USPQ2d 1225 and *Brenner v. Manson* 148 USPQ 689 to support her conclusion.

Applicants respectfully submit that the Examiner, in asserting that the claimed peptide is only useful for further research, is in a sense labeling the claimed peptide a "research tool". An assessment that focuses on whether an invention is useful only in a research setting does not address whether the invention is in fact "useful" in a patent sense. Many research tools such as gas chromatographs, screening assays, and nucleotide sequencing techniques have a clear, specific and unquestionable utility (they are useful in analyzing compounds). See MPEP 2107.01. Furthermore, it has been established that usefulness in patent law, and in particular in the context of pharmaceutical inventions, necessarily includes the expectation of further research and development. See MPEP 2107. 01 III and *In re Brana* 34 USPQ2d 1436. Accordingly, a research tool can not automatically be assumed to be without utility.

The purpose of the patent system is to promote the useful

arts. The utility of "research tools" and pharmaceutical inventions in early development has been frequently addressed by the courts.

The situation in the instant case is analogous to that of *Cross v. Iizuka* (MPEP 2107.01 III and 224 USPQ 739). In *Cross*, the Federal Circuit affirmed a finding by the Board of Patent Appeals and Interferences that a pharmacological utility had been disclosed in the application of one party to an interference proceeding. Cross had challenged the evidence in Iizuka's specification that supported the claimed utility. In *Cross*, the Federal Circuit commented on the significance of data from *in vitro* testing that showed pharmacological activity:

> We perceive no insurmountable difficulty, under appropriate circumstances, in finding that the first link in the screening chain, *in vitro* testing, may establish a practical utility for the compound in question. Successful *in vitro* testing will marshal resources and direct the expenditure of effort to further *in vivo* testing of the most potent compounds, thereby providing an immediate benefit to the public, analogous to the benefit provided by the showing of an *in vivo* utility.

Thus, even if one of skill in the art followed the Examiner's method for the discovery of biomarkers and considered the instant invention to be only a "first step", it (the claimed peptide) would still be considered to have practical utility according to legal precedent. The disclosed link between the claimed peptide (amino acid residues 2-18 of SEQ ID NO:1) and Alzheimer's disease will concentrate resources and effort into this peptide, thereby providing immediate benefit to the public, especially the elderly population at risk for the development of Alzheimer's disease.

The Federal Circuit again addressed the utility requirement in *Scott v. Finney* (MPEP 2107.01 III and 32 USPQ2d 1115) and *In re Brana* (MPEP 2107.01 III and 34 USPQ2d 1436). The court found that therapeutic utility under the patent laws is not to be confused with the requirements of the FDA with regard to the safety and efficacy of drugs to be marketed in the United States. The court stated:

> Usefulness in patent law, and in particular in the context of pharmaceutical inventions, necessarily includes the expectation of further research and development. The stage at which an invention in this field becomes useful is well before it is ready to be administered to humans. Were we to

require Phase II testing in order to prove utility, the associated costs would prevent many companies from obtaining patent protection on promising new inventions, thereby eliminating an incentive to pursue, through research and development, potential cures in many crucial areas such as the treatment of cancer.

The identification of a protein/peptide showing differential expression in Alzheimer's disease relative to an age-matched control population puts a researcher one step closer to understanding the pathogenesis of Alzheimer's disease and thus, also one step closer to improved diagnosis and treatment of Alzheimer's disease. There is no question that improved diagnosis and treatment of Alzheimer's disease provides a tangible benefit to society; especially for the elderly population susceptible to the development of Alzheimer's disease. Thus, the claimed peptide (amino acid residues 2-18 of SEQ ID NO:1) has a "real-world" use as is, in its currently available form.

Furthermore, the instant invention provides a mass spectral profile (shown in Figure 2) of the claimed peptide (amino acid residues 2-18 of SEQ ID NO:1) which is intended to be used as a reference such that the claimed peptide may be identified in

unknown samples by comparison of mass spectral profiles (profile shown in Figure 2 to profiles obtained from unknown samples), thus linking samples to Alzheimer's disease based upon the presence of the claimed peptide.

In conclusion, based upon all of the above arguments (and those presented in previous responses), Applicants respectfully submit that one of ordinary skill in the art would immediately appreciate why Applicants regard the claimed biopolymer marker (amino acid residues 2-18 of SEQ ID NO:1) as useful.

Accordingly, Applicants assert that the claimed invention has both a specific and a well-established utility and respectfully request that this rejection under 35 USC 101 now be withdrawn.

Rejection under 35 USC 112, first paragraph

Claim 1, as presented on October 13, 2005, remains rejected under 35 USC 112, first paragraph. Specifically, the Examiner asserts that since the claimed invention is not supported by either a clear asserted utility or a well established utility, one skilled in the art would clearly not know how to use the claimed invention.

Applicants respectfully disagree with the Examiner's assertions.

It has been established by prior arguments in the instant response that the claimed invention has both a clear asserted utility and a well established utility. Applicants assert that one of skill in the art would know how to use the claimed biopolymer marker (amino acid residues 2-18 of SEQ ID NO:1) as a marker for Alzheimer's disease; therefore, Applicants respectfully request that this rejection under 35 USC 112, first paragraph now be withdrawn.

CONCLUSION

In light of the foregoing remarks, amendment to the specification and amendments to the claims, it is respectfully submitted that the Examiner will now find the claims of the application allowable. Favorable reconsideration of the application is courteously requested.

Respectfully submitted,

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